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Evaluation of a selective management strategy of patients with primary cystic neoplasms of the pancreas

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ABSTRACT

Background: Recent studies have shown that a selective group of patients with primary cystic neoplasms of the pancreas can be managed conservatively by radiological follow-up. The aim of this study was to analyze if such a strategy is efficient and safe.

Patients and methods: A retrospective analyses was performed of patients who underwent resection between January 1992 and January 2006 for primary cystic neoplasms of the pancreas in an era of aggressive management (i.e. all patients underwent resection) in order to analyze if the selective algorithm as proposed by the Memorial Sloan-Kettering Cancer Center is efficient and safe.

Results: One hundred patients underwent a resection for pancreatic cysts. Thirty-five percent of the patients with symptomatic cysts had a (pre)malignant lesion compared with 15% of the patients with an incidental cysts. In hospital mortality occurred in 1% of the patients and a postoperative complications in 39%. The Memorial Sloan-Kettering Cancer Center nomogram was able to correctly identify all patients with a benign incidental cyst.

Conclusion: A selective management strategy can be implemented and algorithm proposed by the Memorial Sloan-Kettering Cancer Center nomogram is safe and efficient.

1. Introduction

Surgeons are increasingly being asked for the surgical management of patients with cystic neoplasms.[1] Most cystic lesions of the pancreas are benign and only a minority require resection. Computed tomography is the imaging modality of choice for pancreatic neoplasm including primary cystic neoplasms and regional guidelines were established since 1997.[2]

Primary cystic neoplasms of the pancreas consist of several pathological entities which include serous cystic neoplasms (SCNs), mucinous cystic neoplasms (MCNs), intra-ductal papillary mucinous neoplasm (IPMNs), solid pseudopapillary neoplasms (SPNs) and various other extremely rare cystic neoplasms (i.e. cystic islet cell neoplasms, teratomas, lympho-epithelial neoplasms).

Serous cystic neoplasms are cysts which are lined by serous cells and are considered to be uniformly benign except for a few reported cases.[3] Mucinous cystic neoplasms are potentially malignant and IPMNs of the pancreas should also be considered of malignant potential. Finally, solid pseudopapillary neoplasms of the pancreas are rare neoplasms that predominate in women. This neoplasm is unique because, although it has a histologically malignant appearance, its biologic behavior is usually much less virulent.[4]

The appropriate management of primary cystic lesions is controversial. In the past most authors recommended an aggressive management strategy because of the unknown natural history and the diagnostic uncertainty of these pancreatic cysts.[5] Several recent reports have recommended a more selective approach toward primary pancreatic neoplasms because improved radiological imaging allows the identification of groups of patients with low risk of malignancy.[6–8] The aim of the present study was to analyze if a selective approach would have been safe and efficient when applied to a cohort of aggressively managed patients.

2. Patients and methods

Patients who underwent pancreatic resection between January 1992 and January 2006 from our prospective database were selected. During this time-frame our hospital enforced an aggressive management approach and offered a resection to all patients with a primary cystic neoplasms which were referred to us. This policy was used because of the limited evidence in the literature

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concerning the sensitivity and specificity of diagnostic imaging modalities and regarding a wait-and-see approach. Procedures included (pylorus preserving) pancreatoduodenectomy ($n = 603$), and total or left pancreatectomy ($n = 129$). Beger and Frey procedures were excluded. All consecutive patients with pathologically proven primary cystic neoplasms of the pancreas formed the study group. In order to analyze whether or not the resection rate has increased, patients with primary cystic neoplasms were compared with the patients who underwent resection for all other solid pancreatic neoplasms throughout the years.

The diagnostic work-up used for pancreatic neoplasms generally consisted of orienting ultrasound (US) followed by computed tomography (CT).[2] Endoscopic retrograde cholangiopancreaticography (ERCP) is generally performed in jaundiced patients to alleviate symptoms. Endoscopic ultrasonography (EUS) is performed when no tumor is found on CT scan or when there is doubt between a pseudocysts or primary pancreatic neoplasm. A EUS guided aspiration with fluid analysis is generally not preformed. Finally, diagnostic laparoscopy (DL) was routinely performed in the earlier years as final step in staging as part of a longitudinal study. Serum tumor markers were seldom used and not analyzed in the present study. The findings were discussed in a multidisciplinary team and patients were generally classified as having a benign cyst, a (pre) malignant cyst or indeterminate.

The patient records were used to collect demographic, clinical, operative and pathological data. The preoperative data included age at presentation, sex, symptoms, imaging and clinical diagnosis. The surgical parameters analyzed included the location of the neoplasm and the type of procedure performed, the postoperative complications and hospital stay. The definitions of complications used for the present study have been reported previously.[9,10] In short, pancreatic fistula was defined as abdominal drain fluid with amylase levels three times the normal serum levels. Delayed gastric emptying was defined as either the need for nasogastric intubation for 10 days or more or the inability to tolerate regular food before or on the 14th postoperative day. In-hospital mortality was defined as death during hospital stay including death during re-admittance within 30 days after discharge.

The histopathological data analyzed comprised the size of the neoplasm, histological features suggestive of malignancy and status of the resection margins. Tumors were considered malignant in case of in situ or invasive malignancy. Al resection specimens were reexamined and classified according to the recent WHO criteria.[11] The follow-up data was recorded through review of the hospital records, the outpatient visits and telephonic interview.

The present study retrospectively applied the algorithm (Fig. 1) proposed by the Memorial Sloan-Kettering Cancer Center (MSKCC)[7] in order to analyze if a selective management strategy could have been implemented in the patients who underwent an aggressive management strategy which was enforced during the study period. This aggressive approach was enforced by all surgeons because of the limited evidence at the time for a selective management strategy. We cross-referenced the operative database with the to ensure that the aggressive approach was implemented.

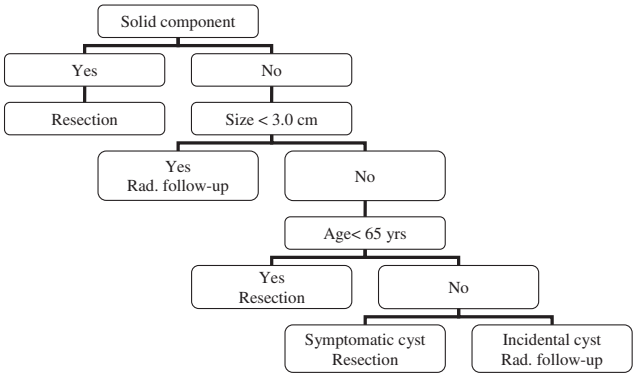

Fig. 1. Decision tree as adapted from Memorial Sloan-Kettering Cancer Center.[7]

Table 1
General characteristics.

	($n = 100$)
Gender	
Male/female	23/77
Median age (range)	56 (13–84)
Symptoms	
Pain	66
Weight loss	30
Nausea	19
Vomiting	10
Jaundice	12
No. of patients with a history of chronic pancreatitis	13

Data analyses were performed using SPSS® software (SPSS, Chicago, Illinois, USA). A p value of less than 0.05 was considered statistically significant. Correlation analysis was performed using the Pearson's correlation coefficient or the Spearman's correlation coefficient depending on the data distribution. Univariate analysis was performed using Pearson's χ^2 test to determine which variables were statistically significant. Fisher's exact test was used when a table had a cell with an expected frequency of less than five. For continuous data the unpaired *t*-test and the Mann–Whitney test were used were appropriate.

3. Results

One thousand and thirty-five patients presented with a potentially resectable pancreatic neoplasm. Eight hundred patients underwent surgery. One hundred out of 732 patients (13.7%) underwent a resection for pancreatic neoplasms for a pathologically proven primary neoplasm of the pancreas and formed the study group (Table 1). The remaining patients ($n = 632$) had other malignant or benign neoplasms or underwent drainage of a pseudocyst ($n = 68$). These patients were excluded from further analysis. One hundred and eighteen patient underwent transgastric endoscopic drainage and 118 patients were managed conservatively in an outpatient follow-up setting. These patients were also excluded from further analysis.

3.1. Diagnostic work-up

After discussion in a multidisciplinary team in a majority of patients there was agreement that a cyst was present but it was uncertain whether the cyst was serous or mucinous.

3.2. Perioperative parameters

One patient in the overall cohort died (Table 2). This patient underwent a pancreatoduodenectomy and died due to uncontrollable delayed massive hemorrhage after unsuccessful coiling of the gastroduodenal artery and eventually had a SCN after pathological evaluation.

Table 2
Perioperative parameters.

	($n = 100$)
Surgical procedures	
Distal pancreatectomy	39
Pylorus-preserving pancreatoduodenectomy	41
Resection of uncinate process	1
Kausch-Whipple Procedure	7
Total pancreatectomy	6
Central pancreatectomy	6
Previous cystogastrostomy	2
Median operative time (range)	3 h 52 min (40 min–9 h 48 min)
Splenectomy[a]	33/51 (65)
Complications (overall)	39
Surgical	27
Pancreaticojejunostomy leakage	4
Hepaticojejunostomy leakage	2
Bleeding	4
Abscess	6
Wound infection	2
Delayed gastric emptying	6
Other	9
Systemic	15
Pulmonal	9
Renal	6
No. patient who underwent relaparotomy	6
Median postoperative hospital stay (range)	13 days (5–111)
Hospital mortality	1

[a] Analysis of patients who underwent distal pancreatectomy, total pancreatectomy and central pancreatectomy.

3.3. Pathology & follow-up

Most patient had a SCN ($n = 32$) follow by MCN ($n = 30$), IPMN ($n = 26$) and SPN ($n = 12$) (Table 3). The mean follow-up was 45 months and ranged from 27 months to 173 months.

3.4. Evaluation of a selective management strategy

Analysis of symptomatic versus incidental cysts found that the size of the cyst was comparable in these groups (Table 4). Overall 22 patients had SCN with symptoms and 10 patients without symptoms. Four patients with an incidental cyst turned out to have frank malignant disease at pathology consisting of IMPN ($n = 3$) and MCN ($n = 1$). The number of patients with a cyst smaller than 3 cm was also comparable between these patients. Overall, 34 patients had a cyst smaller than 3 cm and 8 of these had malignant disease. Eight of these patients with malignant disease had a solid component on CT and were excluded according the algorithm as proposed by the MSKCC. Thus, using the algorithm proposed by the MSKCC, none of the 100 patients with a malignant cyst and would have been managed conservatively by radiological follow-up.

Table 3
Pathology.

	($n = 100$)
Serous Cystic Neoplasm	32
Mucinous Cystic Neoplasms	30
Benign	14
Malignant	16
Intra-ductal Papillary Mucinous Neoplasm	26
Benign	15
Borderline	2
Malignant	9
Solid Pseudopapillary Neoplasm	12
Median neoplasm size in centimeters (range)[a]	5.0 (1.1–25)
R0 resection	81

Numbers between parentheses are percentages unless indicated otherwise.
[a] Size consists of longest axis. Tumors are classifies according to the WHO histopathological classification.

Table 4
The association between cysts <3 cm and malignancy.

	Malignant ($n = 30$)	Benign ($n = 70$)	p
Preoperative no. of patients with cyst <3 cm on CT	8 (27)	26 (37)	0.311[a]
No. of patients with a solid component in cyst	8 (27)	10 (14)	0.162[a]
No. of patients remaining after excluding those with a solid component on CT	0	16 (23)	0.002[b]

Numbers between parentheses are percentages.
[a] χ^2.
[b] Fisher's exact test.

4. Discussion

The present study shows that a conservative management strategy by radiological follow-up is feasible in selected patients using the algorithm proposed by the MSKCC. In this algorithm patients with small asymptomatic cystic neoplasms smaller than 3 cm with no solid component can be monitored safely with virtually no risk of malignancy.

Pancreatic SCNs have virtually no malignant potential and there are only ten reports in literature of malignant SCNs.[3] If asymptomatic, they can almost certainly be observed safely, especially when they occur in the head of the pancreas in an older individual who would otherwise require a pancreaticoduodenectomy.[12] However, this strategy has not been thoroughly evaluated. If symptomatic, most patients require resection since most symptomatic lesions will not be amenable to "simple" enucleation because this procedure is associated with a relatively high morbidity and mortality rate compared to resection.[12]

The vast majority of MCNs are not true invasive adenocarcinoma but mucinous cystadenomas that may harbor carcinoma-in-situ. The time course of progression from benign to malignant has not been clearly determined. If resected these patients are all potentially cured. In contrast, malignant MCNs with an invasive component behave very similar to ductal adenocarcinoma. Although the older literature suggested that malignant MCNs are less malignant than other pancreatic cancers, these reports probably included those MCNs with only dysplasia or PanIN type lesions, thus biasing the survival of true malignant MCNs.[13]

The 5-year survival rate after resection for MCNs varies from 15% to 70% in the literatures.[13,14] Survival disparity in MCNs was attributed to difficulties and differences in the histopathologic classification of these mucinous cystic tumors.[3] The frequency of malignant transformation of branch duct IPMNs ranges from 6% to 46% while that of main duct IPMN is approximately 60%.[15–17] The overall 5-year survival rate of IPMNs is approximately 40–60% with no significant difference between main duct and branch duct.[18,19]

Fernández-del Castillo et al.[20] recently proposed an algorithm for the management of incidental cysts. In this algorithm the authors advise a wait-and-see strategy for incidental cysts smaller than or equal to 2 cm based on the fact that 4% of these cyst are malignant. However the authors also pointed out that up to 50% of these patients had premalignant disease including IPMNs and MCNs. A study by Walsh et al.[8] prospectively observed all patients with an asymptomatic cyst and a negative cyst aspirate defined as having no mucin and CEA < 200 U/L in the aspirate. The authors found that a nonoperative treatment strategy was more often

performed in older patients and patients with a larger cyst. The present study used the algorithm from the MSKCC since this study is the largest to date which analyses the safety and efficacy of a selective approach for primary cystic neoplasms of the pancreas. One major drawback of the study is the fact that follow-up was only 2 years. These tumors are generally slow growing and it can take decades to develop frank malignancy so the safety of the decision to observe has yet to be proven. Another drawback is the fact that the algorithm was created on a large series of patients, most of which did not undergo resection, and therefore include many cysts that were undiagnosed and probably were not neoplastic.

One drawback of the present study is that only patients with proven primary cystic neoplasms were included. Patients with an asymptomatic benign pancreatic cysts (e.g. small pseudocysts) were not included. Therefore the study does not have the true denominator of pancreatic cysts. On the other hand the present study does thoroughly test the MSKCC algorithm is by solely including patients with proven primary neoplastic cysts since most of the patients in the MSKCC algorithm did not undergo resection and therefore also include many cysts that were undiagnosed and probably not neoplastic. The present study found that no patient with a malignancy would have been missed when applied to patient with a proven primary pancreatic cyst.

The algorithm could possible improve if more IPMN characteristics were included in the decision tree such as guidelines proposed by the International Association of Pancreatology (IAP).[21] The IAP guideline for the management of IPMN proposes that neoplasm < 3 cm with high-risk stigmata including mural nodules, dilated main duct and positive cytology should undergo resection. Otherwise it is safe to wait and see in these small neoplasms. This is confirmed by a recent study by Salvia et al.[22] consisting of 109 patients with branch duct IPMN showed that surgery is indicated in only 20% of these patients. Risk factors for malignancy include main duct diameter of >3.5 cm, the presence of mural nodules and a thick wall, a CA 19.9 > 25 U/L and the presence of any symptom including recent onset diabetes. The remaining 80% of the patients underwent radiological follow-up but again the follow-up was limited in this study.

In conclusion, the present study shows that a selective approach is appropriate in balancing the risk of malignancy with the risk of mortality. Intensive follow-up is important since the safety of such a selective management strategy has not yet been proven. The IAP recommends that radiological follow-up by means of MRI or thin slice CT should occur at every 6–12 months for neoplasms between 1 and 2 cm and every 3–6 months for neoplasms between 2 and 3 cm. The interval of follow-up can be lengthened after 2 years of no change.

Conflict of interest
None declared.

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Ethical approval
Not applicable.

Author contribution

S.M.M. de Castro: Study design, data analysis and writing
J.T. Houwert: Data collections and data analysis
N.A. van der Gaag: Data collections and data analysis
O.R.C. Busch: Writing
T.M. van Gulik: Writing
D.J. Gouma: Writing

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